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Enantioselective Total Synthesis of (+)-Methoxystemofoline and (+)-Isomethoxystemofoline

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The first enantioselective total synthesis of (+)-methoxystemofoline (2) and (+)-isomethoxystemofoline (3) is reported. The synthesis employed the halide-assisted bromotropanone method that we developed recently to construct the core structure, and Overman’s strategy for the implementation of the butenolide moiety. Through this work, the structure of methoxystemofoline was revised as 2 with an E-alkene, and its absolute configuration was established.

Methoxystemofoline (2) was isolated in 1991 by Xu and co-workers from the roots of S. parviflora Wright, C. H.2 The structure of methoxystemofoline (2) was elucidated by MS and spectroscopic analyses,2 while its absolute configuration remains unknown. Recently, Pyne and co-workers disclosed the semisyntheses of several stemofoline alkaloids9 including isomethoxystemofoline (3)6a starting from (11Z)-1′2′-didehydrostemofoline. The achievement allowed them ready access to several stemofoline alkaloids and analogues, and to reveal acetylcholinesterase inhibitory activity of those alkaloids.6a,10,11 Our retrosynthetic analysis of methoxystemofoline (2/3) is delineated in Scheme 1. The retro-vinylogous aldol disconnection,6,7 resulted in vinylogous lithium enolate 4 and the core structure 5. The latter could be synthesized from 6 by a cross-metathesis (CM) reaction.12 The tropan-3-one derivative 6 could be prepared from keto-lactam 7 by the method that we developed recently.11

Scheme 1. Retrosynthetic analysis of methoxystemofoline.

The synthesis started with (S)-α-hydroxyγ-lactone 8. O-benzylolation and aminolysis gave hydroxy amide 9 in 81% overall yield (Scheme 2). Oxidation of 9 with Dess-Martin periodinane13 afforded a tautomeric mixture of aldehyde-amide and hemiaminal. The mixture was refluxed in MeOH in the presence of silica gel to convert the former to the latter that was acetylation to yield acetate 10 as a 1:3:1 diastereomeric mixture in 74% yield over three steps. Treatment of 10 with silyl enol ether of acetone and TMSOTf in CH2Cl2 yielded the α-amidoalkylation14 products. The tert-butylidimethylsilyl (TBDMS) group did not survive in these conditions and resilylation of the primary alcohol was required to afford the desired cis-lactam 7 in 72% yield, along with a small amount of the trans isomer. The stereochemistry of the minor diastereomer of 7 was determined by NOESY experiments. Formation of the requisite troparone structure 11 was accomplished smoothly using the method that we...
We next investigated the regioselective C-C bond formations at α and α’ positions of the ketone of tropanone 6 (Scheme 3). Successive treatment of 6 with LDA and methyl pyruvate yielded the desired product 12 in 62% along with a small amount of undesired regioisomer 13 (16%) and some recovered starting material (17%). Hydration of 12 with POCI₃ in the presence of pyridine produced the desired Z-isomer (Z)-14 as a major product in 60% yield. Desilylation of (Z)-14 under acidic conditions (p-TsOH, acetone, 50 °C) followed by bromination with Ph₃P and CBr₄ afforded bromide 16. 16 cyclized easily when treated with NaOMe in THF at 0 °C to give the tricyclic product (Z)-17 in 68% yield.

For the side chain elongation, the hydrochloride salt of (Z)-17 was heated with (Z)-1,4-dimethoxybut-2-ene in the presence of Grubbs’ 2nd generation catalyst to afford the desired cross-coupling product 18 in 56% yield (E/Z = 6.5:1). Isomerization of tetrasubstituted double bond occurred under the reaction conditions and a small amount of 19 (14%) was also obtained. Hydrogenation of 18 proceeded smoothly to give compound 20 in 85% yield. The structure of 20 was confirmed by single crystal X-ray analysis. Silylation of 20 with TMS-imid. at 130 °C led to ester 21 in 83% yield. DIBAL-H reduction of the ester group of 21 followed by Swern oxidation produced aldehyde 22 in 83% yield. The stereochemistry α to the aldehyde group is wrong for the natural product. Hence, aldehyde 22 was epimerized by treating it with DBU in toluene at 100 °C to afford the desired diastereomer 5 (S/22 = 12:1).

Scheme 4. Synthesis of the advanced tetracyclic core 5. Reagents and conditions: (a) 2 N HCl, MeOH; then (Z)-1,4-dimethoxybut-2-ene, Grubbs catalyst, 2nd generation, toluene, 60 °C; (b) Pd/C, H₂, MeOH, rt, 24 h; then 2 N HCl, 48 h; (c) TMS-imid., 130 °C; (d) DIBAL-H, CH₂Cl₂, −78 °C; (e) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, −78 °C; (f) DBU, toluene, 100 °C.

With compound 5 in hand, Overman’s strategy was adopted for the installation of the butenolide moiety.

### Scheme 2. Synthesis of tropan-3-one derivative 6.

Reagents and conditions: (a) Ag₂O, BnBr, rt; (b) TBDMSCOCH₂CH₂NH₂, MeOH, rt; (c) Dess-Martin periodinane, CH₂Cl₂, rt; (d) MeOH, silica gel, reflux; (e) Ac₂O, Et₃N, DMAP, CH₂Cl₂, rt; (f) silyl enol ether of acetoacetate, TMSOTf, CH₂Cl₂, −78 °C - rt; (g) imidazole, TBDMSCl, rt; (h) TMSOTf, Et₃N, CH₂Cl₂, 0 °C; (i) TEO, DTBMP, ZnBr₂, CH₂Cl₂, −78 °C - rt; (j) ACCN, allyl(–Bu)Sn, toluene, 85 °C.

### Scheme 3. Construction of the functionalized tricyclic core (Z)-17.

Reagents and conditions: (a) LDA, methyl pyruvate, THF, −78 °C; (b) POCI₃, pyridine, 0 °C - rt; (c) p-TsOH, acetone, 50 °C; (d) Ph₃P, CBr₄, CH₂Cl₂, 0 °C; (e) NaOMe, THF, 0 °C.

### Scheme 4. Synthesis of the advanced tetracyclic core 5.

Reagents and conditions: (a) 2 N HCl, MeOH; then (Z)-1,4-dimethoxybut-2-ene, Grubbs catalyst, 2nd generation, toluene, 60 °C; (b) Pd/C, H₂, MeOH, rt, 24 h; then 2 N HCl, 48 h; (c) TMS-imid., 130 °C; (d) DIBAL-H, CH₂Cl₂, −78 °C; (e) (COCl)₂, DMSO, CH₂Cl₂, Et₃N, −78 °C; (f) DBU, toluene, 100 °C.

With compound 5 in hand, Overman’s strategy was adopted for the installation of the butenolide moiety.
aldehydes 5 was reacted with vinylogous lithium enolate 4 at −78 °C and the resulting adducts were treated with HCl in MeOH/CHCl₃ to give the vinylogous aldol adduct 23 as a mixture of stereoisomers (Scheme 5). Oxidation of 23 with IBX in DMSO,¹⁹ at rt yielded a diastereomeric mixture 24, which was treated with thiodiphenolate in the presence of DMAP,²⁰ to afford 25 in 65% yield. Finally, heating 25 and P(OMe)₃ at 120 °C provided methoxystemofoline (2) in 30% yield, along with isomethoxystemofoline (3) in 30% yield. The specific rotation [α]D⁻²⁰ = +71.85 (c 0.1, CH₃OH); lit.² [α]D₋²¹ = 75.6 (c 0.037, CH₃OH); 3: [α]D⁻²⁰ = +220–226 (c 0.1, CH₃OH); lit.⁵₄ [α]D⁻²⁵ = +249 (c 0.29, CH₃OH) and spectral data of our synthetic compounds 2 and 3 are consistent with those reported by Xu and Pyne, respectively. Since Pyne and co-workers employed (11Z)-1'-2'-didehydrostemonamine as the starting material for the semisynthesis, their product should have a 11Z stereochemistry (3). Accordingly, the structure of the natural methoxystemofoline suggested by Xu should be revised as 2, with a 11E stereochemistry, and Pyne’s product be named as isomethoxystemofoline (3).

In summary, we have accomplished the first enantioselective total synthesis of (+)-methoxystemofoline (2) and (+)-isomethoxystemofoline (3). The absolute configuration of the natural methoxystemofoline (2) was established as (11E,13E,2S,8S,7R,8S,9R,9a,10S).

Scheme 5. Completion of the total synthesis of methoxystemofoline (2) and isomethoxystemofoline (3). Reagents and conditions: (a) 4, THF, −78 °C; (b) HCl, MeOH/CHCl₃; (c) IBX, DMSO, rt; (d) CS₂Cl₂, DMAP, CHCl₃, −50 °C; (e) P(OMe)₃, 120 °C.

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Notes and references
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